

RESPONSE

1. Rejection of Claims under 35 U.S.C. §102(e)

The Office Action rejected claims 1, 2, 4, 5, 8-15, 17-20 and 23 under 35 U.S.C. §102(e) as being anticipated by Roth et al. (U.S. Patent No. 6,069,134 or U.S. Patent No. 5,747,469). Because the present application was filed prior to November 29, 2000 and has not been voluntarily published, the former version of 35 U.S.C §102(e) applies:

"A person shall be entitled to a patent unless...
(e) the invention was **described** in a patent granted on an application for patent by another filed in the United States **before the invention thereof** by the applicant for patent..." (Emphasis added)

Applicants respectfully submit that applicants invented the subject matter described in the 6,069,134 and 5,747,469 patents which allegedly anticipates the present claimed invention before the effective filing date of the 6,069,134 or 5,747,469 patents. Applicants are submitting herewith (see Section 12, *infra*) an antedating declaration that includes the exhibits required under 37 C.F.R. §1.131 to establish their invention of the subject matter of the rejected claims prior to the effective filing date of the 6,069,134 and 5,747,469 patents. However, although the declaration shows applicants' prior invention of the subject matter of the instant application, according to 37 C.F.R. 1.131(a)(1) such a declaration may not be used to overcome U.S. patents which claim the same patentable invention:

37 C.F.R. §1.131(a):

"Prior invention may not be established under this section if...

(1) The rejection is based upon a U.S. patent...to another or others which claims the same patentable invention as defined in §1.601(n);"

Because the Office Action alleged that the patents both disclosed **and claimed** (Office Action page 2, lines 18-38) several claims of the present application, applicants are precluded from the use of 1.131 affidavits to overcome the 6,069,134 and 5,747,469 patents cited which claim the same patentable invention as the instant application.

2. The Cited Patents Claim the Same Patentable Invention as Defined in 37 C.F.R

§1.601(n).

The Office Action determined that U.S. Patent No. 6,069,134 and U.S. Patent No. 5,747,469 disclose and claim the subject matter claimed in the present application.

Accordingly, 37 C.F.R. §1.601(n) states:

"Invention "A" is the same patentable invention as an invention "B" when invention "A" is the same as (35 U.S.C. 102) or is obvious (35 U.S.C. 103) in view of invention "B" assuming invention "B" is prior art with respect to invention "A". Invention "A" is a separate patentable invention with respect to invention "B" when invention "A" is new (35 U.S.C. 102) and non-obvious (35 U.S.C. 103) in view of invention "B" assuming invention "B" is prior art with respect to invention "A".

The Office Action held that the 6,069,134 or 5,747,469 patent disclosed and claimed claim 1 of the instant application, referring specifically to patented claim 3 among others. It further held that claims 10-13 of the patents claim the subject matter of claim 4 of the instant application, that patent claims 29+ recite the same subject matter as application claims 9 and 10, and that application claims 17-20 and 23 are anticipated by patent claims 54+ (Office Action page 2). Accordingly, applicants respectfully direct the examiner to MPEP 2301.02 which states that

“an interference exists between...an application and a patent, if at least one claim from each would have anticipated or rendered obvious the subject matter of at least one claim of the other.”

3. An Interference Exists between the Present Application and the Cited Patents

Applicants respectfully contend that an interference exists between the patents cited in the Office Action and the instant application because at least one claim of the 5,747,469 patent and the 6,069,134 patent, respectively, anticipates at least one claim of the instant application. Similarly, at least one claim of the instant application anticipates at least one claim of the 5,747,469 and 6,069,134 patent, respectively. Thus, for instance, claim 1 of the 6,069,134 patent reads as follows:

"1. A method of killing a tumor cell in a tumor of a human cancer patient, the method comprising the steps of:
(a) introducing into said tumor an effective amount of polynucleotides encoding a functionally active p53;
(b) expressing p53 in said tumor cell, thereby enhancing the sensitivity of said tumor cell expressing said p53 to a first DNA damaging agent, and
(c) contacting said tumor with a first DNA damaging agent, thereby killing said tumor cell,"

while claim 1 of the present application reads:

"1. A method of increasing the therapeutic effect of a cancer therapy, comprising the steps of:
delivering a wild-type p53 gene to a tumor cell which is deficient in its wild-type p53 gene, effecting the expression of said wild-type p53 gene in said tumor cell, and
subjecting said tumor cell to said cancer therapy."

According to the claim construction by the Board of Patent Appeals and Interferences, claim 1 of the present application is directed to "a method of sensitizing the effect of the subsequently applied cancer treatment to the tumor cell which has been transformed with the wild-type p53 gene where expression of that gene has been effected." (Appeal Decision page 4, lines 12-16). The Board also noted that "the subject matter to which this patent [6,060,134] is directed readily appears to correspond to a

significant degree with the subject matter before us on appeal. Compare claim 1 of the patent with appealed claim 1." (Appeal Decision page 13, lines 5-7). Thus, claim 1 of the 6,069,134 patent and claim 1 of the instant application are directed to virtually identical subject matter, i.e. a method of increasing the sensitivity of a tumor cell to the effect of cancer therapies by introducing the DNA encoding wild-type p53 into the tumor cell and subjecting said tumor cell to said cancer therapy. As a consequence, claim 1 of the instant application anticipates or makes obvious claim 1 of the 6,069,134 patent and vice versa.

Similarly, claim 1 of the 5,747,469 patent reads as follows:

"1. A method of killing a tumor cell in a patient in need thereof, comprising directly administering to said tumor cell therapeutically effective amounts of a viral vector and a DNA damaging agent, wherein said viral vector comprises a DNA sequence encoding p53 operatively linked to a promoter, and wherein expression of said p53 and DNA damage results in the killing of said tumor cell."

While claims 1, 10 and 11 of the present application read as follows:

"1. A method of increasing the therapeutic effect of a cancer therapy, comprising the steps of:
delivering a wild-type p53 gene to a tumor cell which is deficient in its wild-type p53 gene, effecting the expression of said wild-type p53 gene in said tumor cell, and
subjecting said tumor cell to said cancer therapy."

10. The method of claim 1, wherein said wild-type p53 gene is in a vector.

11. The method of claim 10, wherein said vector is selected from the group consisting of adenovirus vector, retroviral vector, adeno-associated virus vector, herpes virus vector, vaccinia virus vector and papilloma virus vector.

Because claim 1 of the 5,747,469 patent and claim 11 of the instant application are directed to substantially identical subject matter, i.e. a method of increasing the

sensitivity of a tumor cell to the effect of cancer therapies by introducing a viral vector comprising the DNA encoding wild-type p53 into the tumor cell and subjecting said tumor cell to said cancer therapy, claim 1 of the 5,747,469 patent anticipates or makes obvious claim 11 of the instant application, and vice versa. Thus, the instant application claims the same patentable invention as U.S. Patent No. 6,069,134 and as U.S. Patent No. 5,747,469, and an interference exists between the present application and the two patents.

4. The Pending Claims Comply With 35 U.S.C. §112 and 35 U.S.C. §135(b)

Applicants respectfully submit that all pending claims in the instant application are fully supported by the specification and have been so since the earliest filing date of April 29, 1994, to which the instant application is entitled. The instant application is a continuation-in-part of application No. 08/248,814, filed May 24, 1994, which is a continuation-in-part of application No. 08/236,221, filed April 29, 1994. The specifications and claims of both parent applications fully support the claims pending in the instant application and there are no outstanding rejections under 35 U.S.C. §112. Furthermore, the requirements of 35 U.S.C. §135(b) are satisfied because no claim in the present application has been added more than one year after the date the 5,747,469 patent issued (May 5, 1998) or more than one year after the date the 6,069,134 patent issued (May 30, 2000). In addition, all presently pending claims contain all material limitations of the originally pending claims.

5. Effective Filing Date of the Application

The present application is a continuation-in-part of application No. 08/248,814, filed May 24, 1994, which is a continuation-in-part of application No. 08/236,221, filed April 29, 1994. According to MPEP 706.02, "any claims which are fully supported under 35 U.S.C. § 112 by the earlier parent application have the effective filing date of that earlier parent application." Applicants respectfully submit that all claims in the instant application are fully supported by the specification and claims of both the 08/248,814 parent application and the 08/236,221 parent application, as shown in the following chart.

Claim	Support in present application	Support in parent 08/248,814	Support in parent 08/236,221
1. A method of increasing the therapeutic effect of a cancer therapy, comprising the steps of: delivering a wild-type p53 gene to a tumor cell which is deficient in its wild-type p53 gene, effecting the expression of said wild-type p53 gene in said tumor cell, and subjecting said tumor cell to said cancer therapy	p 3 ll 8-12, 25-29 p. 4 ll 17-21 p 7 ll 11-15 p 8 ll 4-9, 12-19 p 13 ll 35-39 p 14 l 21 – p 15 l 15 p 23 l 35 – p 26 l 10.	p 3 ll 5-9, 22-26 p 4 ll 14-18 p 7 ll 8-12 p 8 ll 1-6, 9-15 p 13 ll 31-35 p 14 l 24 – p 15 l 12 p 23 l 17 – p 25 l 28.	p 2 l 34 – p 3 l 2 p 3 ll 15-19 p 4 ll 7-11 p 7 ll 1-5, 30-35 p 13 ll 20-24 p 14 l 11 – p 15 l 5 p 23 l 1 – p 24 l 33
2. A method of increasing the therapeutic effect of a cancer therapy, comprising the steps of: delivering a wild-type p53 protein to a tumor cell which is deficient in its wild-type p53 gene, and subjecting said tumor cell to said cancer therapy	p 20 ll 20-34	p 20 ll 15-29	p 19 l 35 – p 20 l 13
4. The method of claim 1 wherein said cancer therapy is radiation therapy	p 3 ll 13-14 p 8 ll 7-9 p 14 ll 24-25 p 27 l 25 p 28 l 30 p 30 l 23	p 3 ll 10-11 p 8 ll 4-6 p 13 l 44 – p 14 l 2 p 26 ll 18-19 p 27 ll 6-7, 27-28 p 28 ll 11-12	p 3 ll 3-4 p 7 ll 33-35 p 14 ll 14-15 p 26 l 26 p 27 l 11, 131 p 29 l 24
5. The method of claim 1 wherein said cancer therapy is chemotherapy	p 3 ll 13-15 p 23 l 35 – p 25 l 31 p 27 ll 24-25 p 28 ll 9-10, 29-30 p 30 ll 22-23	p 3 ll 10-13 p 23 l 17 – p 25 l 13 p 26 ll 18-19 p 27 ll 6-7, 27-28 p 28 ll 11-12	p 3 ll 3-5 p 23 l 1 – p 24 l 33 p 26 ll 25-26 p 27 ll 10-11, 30-31 p 29 ll 23-24
6. The method of claim 1 wherein said cancer therapy is immunotherapy	p 3 ll 13-15 p 14 ll 3-6, 133 – p 15 l 15	p 3 ll 10-12 p 13 l 44 – p 14 l 13 p 14 l 30 – p 15 l 12	p 3 ll 3-5 p 13 ll 33-36 p 14 l 23 – p 15 l 5
7. The method of claim 1 wherein said cancer therapy is cryotherapy	p 3 ll 13-16 p 14 ll 3-6	p 8 ll 10-13 p 13 l 44 – p 14 l 13	p 3 ll 3-6 p 13 ll 33-36

	p 27 ll 24-25 p 28 ll 9-11, 29-31 p 30 ll 22-23	p 26 ll 18-20 p 27 ll 6-7, 27-29 p 28 ll 11-13	p 26 ll 1-3, 25-26 p 27 ll 10-12, 30-32 p 29 ll 23-24
8. The method of claim 1 wherein said cancer therapy is hyperthermia	p 3 ll 13-16 p 14 ll 3-6 p 27 ll 24-26 p 28 ll 9-11, 29-31 p 30 ll 22-24	p 3 ll 10-13 p 13 ll 144 – p 14 ll 13 p 26 ll 18-20 p 28 ll 11-13 p 29 ll 6-8, 27-29	p 3 ll 3-6 p 13 ll 33-36 p 26 ll 1-3, 25-27 p 27 ll 10-12, 30-32 p 29 ll 23-25
9. The method of claim 1, wherein said tumor cell is selected from the group consisting of leukemia cell, lymphoma tumor cell, ovarian carcinoma cell, osteogenic sarcoma cell, lung carcinoma cell, colorectal carcinoma cell, hepatocellular carcinoma cell, glioblastoma cell, prostate cancer cell, pancreatic cancer cell, gastric cancer cell, esophageal cancer cell, anal cancer cell, biliary cancer cell, and urogenital cancer cell.	p 3 ll 16-24 p 27 ll 9-14	p 3 ll 13-21 p 26 ll 27-32	p 3 ll 6-14 p 26 ll 10-15
10. The method of claim 1, wherein said wild-type p53 gene is in a vector.	p 3 ll 32-33 p 16 ll 17-18 p 17 ll 3-8	p 3 ll 29-30 p 16 ll 14-15, 136 – p 17 ll 15	p 3 ll 22-23 p 15 ll 34-35 p 16 ll 20-25
11. The method of claim 10, wherein said vector is selected from the group consisting of adenovirus vector, retroviral vector, adeno-associated virus vector, herpes virus vector, vaccinia virus vector and papilloma virus vector.	p 7 ll 16-21 p 17 ll 9 – p 19 ll 16	p 7 ll 13-18 p 17 ll 16- p 19 ll 13	p 7 ll 6-11 p 16 ll 126 – p 18 ll 116
12. The method of claim 1, wherein said wild-type p53 gene is coupled to a virus capsid or particle.	p 3 ll 34-35 p 7 ll 21-24 p 19 ll 7-30	p 3 ll 31-32 p 7 ll 18-21 p 19 ll 4-25	p 3 ll 24-25 p 7 ll 11-14 p 18 ll 124 – p 19 ll 19
13. The method of claim 12, wherein said wild-type p53 gene is coupled to said capsid or particle through a polylysine bridge.	p 7 ll 124 p 19 ll 9-10	p 7 ll 121 p 19 ll 6-7	p 7 ll 13-14 p 18 ll 26-27
14. The method of claim 1, wherein said wild-type p53 gene is encapsulated in a liposome.	p 4 ll 1 p 7 ll 25-26 p 19 ll 131 – p 20 ll 17 p 22 ll 9-14 p 23 ll 14-21	p 3 ll 134 p 7 ll 22-23 p 19 ll 126 – p 20 ll 12 p 21 ll 27-32 p 22 ll 132 – p 23 ll 13	p 3 ll 127 p 7 ll 15-16 p 19 ll 10-22 p 21 ll 11-16 p 22 ll 16-23
15. The method of claim 1, wherein said wild-type p53 gene is conjugated to a ligand.	p 3 ll 136 p 20 ll 8-18	p 3 ll 133 p 20 ll 3-13	p 3 ll 126 p 19 ll 23-33
16. The method of claim 15, wherein said ligand is an asialoglycoprotein.	p 7 ll 125 p 20 ll 10-12	p 7 ll 122 p 20 ll 5-7	p 7 ll 115 p 19 ll 25-27
17. The method of claim 1, wherein said wild-type p53 gene	p 7 ll 127 p 26 ll 27-34	p 7 ll 124 p 26 ll 9-16	p 7 ll 117 p 25 ll 29-36

is introduced to said tumor cell by direct injection.			
18. The method of claim 1, wherein said wild-type p53 gene is introduced to said tumor cell by intra-arterial infusion.	p 7128 p 20125 p 27133 – p 2819	p 7125 p 20120 p 27115-27	p 7118 p 2014 p 26134 – p 27110
19. The method of claim 1, wherein said wild-type p53 gene is introduced to said tumor cell by intracavitary infusion.	p 7128 p 20125 p 21124 p 28123 – p 2917	p 7125 p 20120 p 2116 p 28115-25	p 7118 p 2014, 126
20. The method of claim 1, wherein said wild-type p53 gene is introduced to said tumor cell by; intravenous infusion	p 7129 p 20125 p 21121	p 7126 p 20120 p 2113	p 7119 p 2014, 123
23. The method of claim 1, wherein said wild-type p53 gene is introduced to said tumor cell in aerosolized preparation.	p 201126-28 p 261127-36	p 201121-23 p 26119-18	p 20115-7 p 25129 – p 2611

Because all pending claims in the present application are fully supported by the specification of not only the instant application but also the specifications of both parent applications, the claims of instant application are entitled to an effective filing date of April 29, 1994.

6. Effective Filing Date of the 5,747,469 and 6,069,134 Patents

The 5,747,469 patent issued on an application that was filed on April 25, 1994, as a continuation-in-part of application 08/145,826, filed October 29, 1993, which is a continuation-in-part of application 07/960,513, filed October 13, 1992, which is a continuation-in-part of application 07/665,538, filed March 6, 1991. In order to determine whether the claims of the 5,747,469 patent are entitled to a filing date earlier than April 25, 1994, it is necessary to examine whether the claims and specification of the parent application fully support the claims of the issued patent under 35 U.S.C. §112. Applicants respectfully note that the identical analysis applies to the 6,069,134 patent which is a divisional of the 5,747,469 patent. Thus, the first question is whether the

08/145,826 application provides full support for the claims in the 5,747,469 and 6,069,134 patents. Applicants respectfully submit that it does not.

The 08/145,826 application has issued as U.S. Patent No. 6,410,010 entitled "Recombinant p53 Adenovirus Compositions". The patent discloses and claims adenoviral vector constructs comprising a cytomegalovirus promoter directing the expression of p53. The adenoviral constructs are disclosed to be useful for restoring normal p53 functions and growth suppression to cells with abnormal p53. While the specification of the 6,410,010 patent which issued on the 08/145,826 application discloses the "astonishing" effects of the constructs on controlling metastatic growth and on the inhibition of tumorigenicity of cancer cells, nowhere does the specification, nor do the claims, provide support for combining the delivery of p53 to a tumor cell with the subsequent application of a cancer treatment to increase the sensitivity of tumor cells to cancer therapies. Because the 6,410,010 patent contains no disclosure of a cancer therapy-sensitizing effect of wild-type p53 when introduced into a tumor cell, or of the combination p53 vectors with DNA damaging agents to induce enhanced tumor cell death or a method of killing a tumor cell comprising expressing wild-type p53 in a tumor cell and contacting the tumor cell with a DNA damaging agent, the 08/145,826 application utterly fails to provide any support under 35 U.S.C. §112 for the claims of the 5,747,469 patent, as well as the 6,069,134 patent directed to the combination of administering wild-type p53 with conventional cancer therapies. Thus, in no case can the earliest effective filing date of both the 5,747,469 patent and the 6,069,134 patent be prior to the filing date of the new continuation-in-part application, April 25, 1994.

7. Compliance With 37 C.F.R. 1.608(a)

37 C.F.R. 1.608(a) provides as follows:

When the effective date of an application is three months or less after the effective filing date of a patent, before an interference will be declared, either the applicant or the applicant's attorney of record shall file a statement alleging that there is a basis upon which the applicant is entitled to a judgment relative to the patentee.

Because the effective filing date of the instant application is April 29, 1994 and the effective filing date of the claims in U.S. Patent No. 6,069,134 and 5,747,469 which interfere with the claims in the present application is April 25, 1994, the effective filing date of the present application is three months or less after the effective filing date of the 6,069,134 and 5,747,469 patents. Thus, the requirements of 37 C.F.R. 1.608(a) are met. Accordingly, applicants respectfully assert that there is a basis upon which applicants are entitled to judgment relative to the patentee. Applicants respectfully refer the Examiner to the enclosed declaration in which it is asserted that applicants are the first inventors of the subject matter of the claims pending in the instant application, namely of a method of increasing the sensitivity of tumor cells to cancer therapies by introducing wild-type p53 into tumor cells followed by the application of a cancer therapy to said tumor cells.

8. Applicants Request that an Interference be Declared

37 C.F.R. 1.607 governs requests for interference by applicants for patent and provides as follows:

- (a) An applicant may seek to have an interference declared between an application and an unexpired patent by,
 - (1) Identifying the patent,
 - (2) Presenting a proposed count,

- (3) Identifying at least one claim in the patent corresponding to the proposed count,
- (4) Presenting at least one claim corresponding to the proposed count or identifying at least one claim already pending in its application that corresponds to the proposed count, and, if any claim of the patent or application identified as corresponding to the proposed count does not correspond exactly to the proposed count, explaining why each such claim corresponds to the proposed count, and
- (5) Applying the terms of any application claim,
 - (i) Identified as corresponding to the count, and
 - (ii) Not previously in the application to the disclosure of the application.
- (6) Explaining how the requirements of 35 U.S.C. 135(b) are met, if the claim presented or identified under paragraph (a)(4) of this section was not present in the application until more than one year after the issue date of the patent.

(1) Accordingly, applicants hereby identify U.S. Patent No. 5,747,469 and U.S. Patent No. 6,069,134 for purposes of requesting an interference with the present application.

- (2) Applicants further propose the following count:

Count 1: A method of increasing the therapeutic effect of a cancer therapy, comprising the steps of delivering a wild-type p53 gene to a tumor cell which is deficient in its wild-type p53 gene, effecting the expression of said wild-type p53 gene in said tumor cell, and subjecting said tumor cell to said cancer therapy.

(3) Claims 1 through 105 in U.S. Patent No. 5,747,469 and claims 1 through 69 of U.S. Patent No. 6,069,134 are hereby identified as corresponding to Count 1.

(4) Claims 1, 4, 5-20 and 23 in the present application are hereby identified as corresponding to Count 1. Claim 1 corresponds exactly to proposed Count 1. Claims 4-20 and 23 depend from claim 1 and introduce additional limitations. Because claims 4-20 and 23 are dependent on claim 1 and introduce only obvious limitations to claim 1, they correspond substantially to Count 1.

(5) All of the claims of the present application identified as corresponding to proposed Count 1 have been pending in the instant application and are fully supported by its disclosure, as evidenced, *inter alia*, by the absence of any outstanding rejections under 35 U.S.C. §112.

(6) All claims identified as corresponding to Count 1 have been pending in the present application prior to one year after the issuance of the 5,747,469 and 6,069,134 patents. Thus, the requirements of 35 U.S.C. §135(b) are met.

9. Rejection of claims 1, 2, 4-15, 17-20 and 23 under 35 U.S.C. § 103(a) over the Interfering Patents

The Office Action rejected claims 1, 2, 4-15, 17-20 and 23 under 35 U.S.C. § 103(a) as being unpatentable over Roth et al. (U.S. Patent No. 6,069,134 or U.S. Patent No. 5,747,469) taken with Moossa et al. (Comp. Text. Oncol., vol. 1 and 2). Applicants respectfully traverse the rejection for the following reasons: As explained in section 1 of this response, according to 37 C.F.R. 1.131(a)(1) an antedating declaration may not be used to overcome U.S. patents which claim the same patentable invention. Thus, applicants are precluded from obtaining an allowance of the claims over U.S. Patent Nos. 6,069,134 and 5,747,469 by the use of a declaration to show prior invention under 37 C.F.R. §1.131 because the patents claim the same patentable invention claimed by the present application. Furthermore, as explained in MPEP §715.05:

"Since 37 CFR 1.131 defines "same patentable invention" in the same way as the interference rules (37 CFR 1.601(n)), the USPTO cannot prevent an applicant from overcoming a reference by a 37 CFR 1.131 affidavit or declaration on the grounds that the reference claims applicant's invention and, at the same time, deny applicant an interference on the

grounds that the claims of the application and those of the reference are not for substantially the same invention."

Because the correct procedure to be followed is the declaration of an interference, the 6,069,134 and 5,747,469 patents are not properly held as prior art references under 35 U.S.C. §102(e) against the instant application. Without the 6,069,134 and 5,747,469 patents as references, Moossa fails to provide any suggestion or motivation to combine conventional cancer therapies with the delivery of wild-type p53 to tumor cells in order to increase the sensitivity of the tumor cells to cancer therapies. Furthermore, the fact that the 6,069,134 and 5,747,469 patents claiming the same invention as the instant application issued to another party is *prima facie* evidence of the nonobviousness of the present invention at the time the instant application was filed. Both patents have an effective filing date four days prior to the effective filing date of the present application, while the information contained in Moossa et al. was available to the public in 1991. Thus, as of April 25, 1994, the invention claimed by both the instant application and the 6,069,134 and 5,747,469 patents was nonobvious over Moossa. Note also that the opinion of the Board of Patent Appeals and Interferences, in holding the present invention nonobvious over the prior art including Moossa, stated that "one of ordinary skill in this art at the time of the invention would have expected that the likely result of combining the therapies of [Cheng and Nabel] with the other types of cancer therapies described by Moossa would have been that the transformed tumor cells would have been more resistant to such cancer therapies." (Appeal Opinion page 10). Thus, the instant invention could not have been obvious to a person of skill in the art at the time the application was filed.

10. Rejection of Claims 1, 2, 4-15, 17-20 and 23 under 35 U.S.C. 103(a)

Claims 1, 2, 4-15, 17-20 and 23 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (US 6,410,010) taken with Moossa. The Office Action alleged that "Zhang et al. disclose administering vectors that restore wildtype p53 function...as a cancer therapy in cells having a mutant or aberrant p53 gene as effective methods of cancer therapy...and where palliative therapy for the patient would have been expected to have been included since (column 16, lines 29+) would indicate (line 57+) inclusion of other palliative therapies." Applicants respectfully traverse the obviousness rejection.

Claims 1, 4-15, 16, 17-20 and 23 of the instant application are directed to a method of increasing the therapeutic effect of a cancer therapy, comprising delivering a wild-type p53 gene to a tumor cell which is deficient in its wild-type p53 gene, effecting the expression of said wild-type p53 gene in said tumor cell, and subjecting said tumor cell to said cancer therapy. Claim 2 is directed to the same method, except for the delivery of wild-type p53 protein to tumor cells. Zhang et al. describe and claim adenoviral-p53 constructs as a means **for restoring growth suppression** in tumor cells (Column 2, lines 55-56) and for **decreasing the rate of proliferation of lung cancer cells** (column 16, lines 40-42). See also the specification section E (p53-Adenovirus Constructs and Tumor Suppression), which shows that the "**tumorigenicity** of the Ad5CMV-p53 treated cells was greatly **inhibited**," and section G (Patients and Treatment Protocols) which states that "it is anticipated that the uptake of the adenovirus constructs by NSCLC cells will **decrease the rate of proliferation** of these cells."

(Emphasis added). Nowhere do Zhang et al. suggest combining the delivery of wild-type p53 to the tumor cells with the application of conventional cancer therapy to increase the therapeutic effect of the cancer therapy. Nor do Zhang describe or suggest using a wild-type p53 gene to make the tumor cells more sensitive to cancer therapies.

In addition, applicants respectfully disagree with the assertion in the Office Action that "palliative therapy for the patient would have been expected to have been included" with the administration of the vectors disclosed in Zhang. The specification at Column 16, lines 45+ clearly shows that the Zhang inventors did not contemplate combining the administration of the p53 vectors with conventional cancer therapies to increase the sensitivity of tumor cells to the cancer treatment. Rather, the specification cautions that "Patients with unresectable endobronchial tumor recurrence that is partially or completely obstructing the airway and that have **failed or are unable to receive external beam radiotherapy will be considered** for this protocol," and "patients **failing brachytherapy would also be eligible to receive gene therapy.**" (Emphasis added).

Thus, the teaching of the Zhang patent explicitly limits the application of the p53 constructs to those patients in whom conventional cancer therapies has been unsuccessful. This is completely the opposite of, and indeed teaches away from, the method of the present invention which teaches combining the administration of wild-type p53 with conventional cancer therapies in order to increase the susceptibility of the tumor cells to those cancer therapies. In this context, the statement in Zhang et al., Column 16, lines 58-60 that "the administration of the viral constructs would **not preclude** the patient from receiving **other palliative therapy if the tumor progresses,**" (emphasis added) evinces nothing more than the inventors' uncertainty of the effectiveness of the p53

constructs and the availability of palliative measures (those affording pain relief without being curative) to those patients in whom the p53 constructs do not effect inhibition of tumor progression.

It is thus evident that the desirability of combining the delivery of p53 to a tumor cell with the subsequent application of a cancer treatment to increase the sensitivity of tumor cells to cancer therapies is neither disclosed nor suggested in Zhang or Moossa. In fact, the disclosure in Zhang does not even make it obvious to try to combine the administration of p53 with conventional cancer therapies, as it seeks to specifically limit the administration of the p53 vectors to only those patients that have already failed conventional therapy, i.e. patients no longer receiving such therapies. This is consistent with the expectation held by persons of ordinary skill in the art at the time the instant application was filed that "rather than an additive or beneficial result, a desensitizing of the tumor cells to the other forms of cancer therapy could result." Board of Patent Appeals and Interferences Opinion, page 11, lines 10-14. Because Zhang in combination with Moossa ostensibly lack any suggestion, recognition, or appreciation of the method of increasing the sensitivity of tumor cells to cancer therapies by introducing wild-type p53 into cancer cells and subjecting the cancer cells to conventional cancer therapy, the present invention could not have been obvious to a person of skill in the art at the time the instant application was filed.

11. Rejection of Claim 16 under 35 U.S.C. §103(a)

Claim 16 has been rejected over Roth et al. (US 6,069,134 or 5,747,469) taken with Moossa et al. (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1,2,4-15, 17-

20 and 23 above and further in view of Wu et al. (US '320); or, Zhang et al. (US 6,410,010) taken with Moossa et al. (Comp. Text. Oncol., vol. 1 and 2) and further in view of Wu et al. Claim 16 is directed to a method of increasing the therapeutic effect of a cancer therapy, comprising the steps of delivering a wild type p53 gene to a tumor cell which is deficient in its wild-type p53 gene, effecting the expression of said wild-type p53 gene in said tumor cell, and subjecting said tumor cell to said cancer therapy, wherein said wild-type p53 gene is conjugated to a ligand, wherein said ligand is asialoglycoprotein. Because claim 16 depends on claims 1 and 15, it includes all of their limitations. As explained in the previous sections, Roth et al. (US 6,069,134 or 5,747,469) are not proper prior art references to the instant invention, whereas neither Moossa et al. (Comp. Text. Oncol., vol. 1 and 2) nor Zhang et al. (US 6,410,010) taken with Moossa et al. (Comp. Text. Oncol., vol. 1 and 2) disclose, suggest or make obvious the combination of the present invention. The fact that Wu et al. disclose a process for in vivo delivery of DNA to a target cell using a complex of asialoglycoprotein for replacement of defective genes does not add anything to the combined disclosures of Zhang and Moossa that would render claim 16 obvious because regardless of teaching conjugating p53 to an asialoglycoprotein ligand, none of these references disclose or suggest combining the administration of wild-type p53 with conventional cancer therapy in order to increase the sensitivity of tumor cells to those conventional cancer therapies. Thus, claim 16 would not have been obvious to a person of ordinary skill in the art over the references cited.

12. Submission of Affidavit under 37 C.F.R. § 1.131

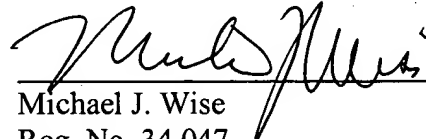
Applicants submitted a supplemental IDS on December 24, 2002, containing an abstract disclosing the administration of p53 vectors with the subsequent administration of cancer therapy. In the event that the disclosure of this abstract were held to anticipate the present invention, applicants are submitting a 37 C.F.R. §1.131 antedating affidavit complete with the required exhibits to show that applicants invented the subject matter claimed in the instant application prior to the publication of the abstract, that is, prior to March, 1994.

13. But for the Interference, the Claims in the Instant Application are Patentable to Applicants

Applicants respectfully submit that all pending claims are patentable to applicants over the prior art, except for the 5,747,469 and 6,069,134 patents which claim the same invention as the present application. It is therefore respectfully requested that an interference proceeding be instituted.

Respectfully submitted,
Perkins Coie LLP

Dated: December 30, 2002

By: 
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VERSION WITH MARKINGS TO SHOW CHANGES

IN THE SPECIFICATION

In the specification:

Please delete the paragraph beginning on page 1, line 3 and ending on line 11, and replace it with the following paragraph:

Cross Reference to Related Application

This application is a continuation-in-part application of U.S. Application No. 08/248,814 [08/236,221], entitled "ENHANCING THE SENSITIVITY OF TUMOR CELLS TO THERAPIES," filed May 24, 1994, which is a continuation-in-part application of U.S. Application No. 08/236,221, entitled "ENHANCING THE SENSITIVITY OF TUMOR CELLS TO THERAPIES," filed April 29, 1994; the disclosure of the above two parent applications are incorporated herein by reference.

CLEAN VERSION

IN THE SPECIFICATION

In the specification:

Please delete the paragraph beginning on page 1, line 3 and ending on line 11, and replace it with the following paragraph:

Cross Reference to Related Application

This application is a continuation-in-part application of U.S. Application No. 08/248,814, entitled "ENHANCING THE SENSITIVITY OF TUMOR CELLS TO THERAPIES," filed May 24, 1994, which is a continuation-in-part application of U.S. Application No. 08/236,221, entitled "ENHANCING THE SENSITIVITY OF TUMOR CELLS TO THERAPIES," filed April 29, 1994; the disclosure of the above two parent applications are incorporated herein by reference.